PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
99,423-A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 40281	21/06/2000	22/06/1999
Applicant		
CV THERAPEUTICS, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/40281

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/16 A61K31/7076 A61K49/00 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. MARUMOTO ET AL.: "Synthesis and coronary vasodilating activity of 2-substituted adenosines" CHEM. PHARM. BULL., vol. 23, no. 4, 1975, pages 759-774, XP002154408 abstract page 768, structures 29j and 29k	1,20
A	EP 0 354 638 A (MEDCO RES INC) 14 February 1990 (1990-02-14) the whole document	1,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	22/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/40281

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0354638 A	14-02-1990	US 5070877 A	10-12-1991
		CA 1305922 A	04-08-1992
		JP 2914454 B	28-06-1999
		JP 3047136 A	28-02-1991
		JP 10114684 A	06-05-1998

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 March 2001 (27.03.01)	
International application No. PCT/US00/40281	**Applicant's or agent's file reference** 99,423-A
International filing date (day/month/year) 21 June 2000 (21.06.00)	**Priority date** (day/month/year) 22 June 1999 (22.06.99)
Applicant ZABLOCKI, Jeff, A. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 January 2001 (10.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Christelle Croci
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

RECEIVED

DEC 2 8 2000

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

AB-K.B.

To:
McDONNELL BOEHNEN HULBERT
& BERGHOFF
Attn. HUGHES, A.B.
300 South Wacker Drive
Chicago, IL 60606
UNITED STATES OF AMERICA

Applicant's or agent's file reference 99,423-A	Date of mailing *(day/month/year)* 22/12/2000
International application No. PCT/US 00/40281	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant CV THERAPEUTICS, INC. et al.	International filing date *(day/month/year)* 21/06/2000

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	John De Bruijn

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
99,423-A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 40281	21/06/2000	22/06/1999
Applicant		
CV THERAPEUTICS, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/40281

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/16 A61K31/7076 A61K49/00 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. MARUMOTO ET AL.: "Synthesis and coronary vasodilating activity of 2-substituted adenosines" CHEM. PHARM. BULL., vol. 23, no. 4, 1975, pages 759-774, XP002154408 abstract page 768, structures 29j and 29k	1,20
A	EP 0 354 638 A (MEDCO RES INC) 14 February 1990 (1990-02-14) the whole document	1,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" eartier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	22/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/40281

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-22 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/40281

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0354638 A	14-02-1990	US 5070877 A	10-12-1991
		CA 1305922 A	04-08-1992
		JP 2914454 B	28-06-1999
		JP 3047136 A	28-02-1991
		JP 10114684 A	06-05-1998

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 00/40281

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/16 A61K31/7076 A61K49/00 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. MARUMOTO ET AL.: "Synthesis and coronary vasodilating activity of 2-substituted adenosines" CHEM. PHARM. BULL., vol. 23, no. 4, 1975, pages 759-774, XP002154408 abstract page 768, structures 29j and 29k	1,20
A	EP 0 354 638 A (MEDCO RES INC) 14 February 1990 (1990-02-14) the whole document	1,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	22/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 00/40281

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0354638 A	14-02-1990	US 5070877 A	10-12-1991
		CA 1305922 A	04-08-1992
		JP 2914454 B	28-06-1999
		JP 3047136 A	28-02-1991
		JP 10114684 A	06-05-1998

10/070796

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
99,423-A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/40281	21/06/2000	22/06/1999
International Patent Classification (IPC) or national classification and IPC C07H19/16		
Applicant CV THERAPEUTICS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/01/2001	12.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Jenn, T Telephone No. +49 89 2399 7348

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/40281

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

3-43	as originally filed			
1,2	as received on	28/06/2001	with letter of	26/06/2001

Claims, No.:

1-25	as originally filed

Drawings, sheets:

1/4-4/4	as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 18,20-22.

because:

   ☒ the said international application, or the said claims Nos. 20-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 18 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17,19-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17,19-25
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17,19,23-25
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

1. The amendments filed with the letter dated June 26, 2001, received on June 28, 2001, introduce subject-matter which extend beyond the content of the application as filed, contrary to Article 34(2) PCT. The amendments concerned are the following:

1.1 Amended claim 1 **(see particularly Item VIII § 3 of this opinion)**:

A compound having the formula as claimed in claim 1, wherein R^3 is selected from "$NR^{20}C(NR^{20})NHR^{22}$" (line 7, new page 47), or wherein substituents are optionally substituted with "$NR^{20}C(NR^{20})NHR^{22}$" (line 14, new page 47) is not disclosed in the application as originally filed which discloses such a compound wherein R^3 is "$NR^{20}C(NR^{20})NHR^{23}$" (line 7, page 44), or wherein substituents are optionally substituted by "$NR^{20}C(NR^{20})NHR^{23}$" (line 14, page 44).

A compound having the formula as claimed in claim 1, wherein the substituents of R^7 are optionally substituted with "$NR^{20}C(NR^{20})NHR^{22}$" (line 13, new page 48) is not disclosed in the application as originally filed which discloses such a compound wherein substituents are optionally substituted by "$NR^{20}C(NR^{20})NHR^{23}$" (l. 11, p. 45).

1.2 Amended claim 8:

A compound according to claim 8 wherein R^7 is selected from "**C_{1-8}** alkyl that is optionally substituted with **one substituent** selected from **halo, CF_3, CN and OR^{20}**" (lines 27-28, new page 51) is not disclosed in the application as originally filed which discloses such a compound wherein R^7 is selected from "**C_{1-5}** alkyl, wherein the alkyl substituent is optionally substituted with **aryl, and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3**" (page 48, lines 22-24).

1.3 Amended claim 9:

A compound according to claim 9 wherein R^7 is selected from "**C_{1-3}** alkyl that is optionally substituted with **one substituent** selected from **halo, CF_3, CN and OR^{20}**" (lines 1-2, new page 52) is not disclosed in the application as originally filed which discloses such a compound wherein R^7 is selected from "**C_{1-5}** alkyl, wherein the alkyl substituent is optionally substituted with **aryl, and wherein each optional aryl substituent is optionally substituted with halo**" (page 48, lines 31-33).

1.4 Amended claim 16:

A compound according to claim 16 wherein R^7 is selected from "**C_{1-3}** alkyl that is optionally substituted with **one substituent** selected from **halo, CF_3, CN and OR^{20}**" (lines 11-12, new page 53) is not disclosed in the application as originally filed

which discloses such a compound wherein R^7 is selected from "C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with **aryl, and wherein each optional aryl substituent is optionally substituted with halo**" (page 50, lines 11-13).

1.5 Amended description:

The same as disclosed in § 1.1 above applies to the corresponding amendments in the description (new page 4, line 16; new page 5, lines 1, 13 and 25).

A compound wherein "when R^1=CH_2OH, then it is most preferred that R^7 is a methyl and R_3 is CO_2Et" (see new page 8, line 29) is not disclosed in the application as originally filed (see original claims 11 and 12 which depend on claim 10).

2. As some of the amendments of the description are not allowable (see above), and as said amendments were not made by the way of **replacement pages** in the manner stipulated by Rule 66.8(a) PCT (see as well the PCT Guidelines Chap. VI-7.2 and 7.3), certain of the allowable amendments of the description cannot be taken into consideration in this report (the numbering of the pages would become confusing).

Therefore, although the amendments of the description from new page 5 (line 27) to new page 8 (line 28), and from new page 8 (line 31) to new page 9 (line 28) do not introduce subject-matter which was not disclosed in the application as originally filed, these amendments are not taken in consideration in this report, nor are taken the allowable amendments of the description on new page 10 (lines 5 and 9), on new page 23 (line 7), on new page 25 (line 15), on new page 26 (line 5 [Obs: "is" should be replaced by "in"]), on new page 29 (line 10), on new page 30 (line 1), on new page 31 (line 1), on new page 34 (line 1), on new page 37 (line 1), and on new page 40 (line 1).

3. Therefore, the present opinion will be given on the subject-matter of claims 1-25 as originally filed, on the subject-matter of amended pages 1-2 of the description as filed with the letter dated June 26, 2001, received on June 28, 2001, which replace the original pages 1-2, and on original pages 3 to 43 of the description.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject-matter of **claim 18** is so unclear (see the grounds for this objection in

Item VIII of this opinion), that no meaningful opinion can be formed on the novelty, inventive step and industrial applicability of said claim.

2. The method as claimed in **claims 20 to 22** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (diagnostic method carried out on the living human or animal body). Consequently, **no opinion** will be formulated **on** the **industrial applicability** of the subject-matter of these claims (Article 34(4)(a)(i) PCT, see also the PCT-guidelines IV-2.4.(d) and IV-2.5); an opinion on novelty and inventive step will be given for the alleged effects of a compound of claim 1 in the method of claims 20 to 22.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

-

Reference is made to the following document:

D1 (R. MARUMOTO et al.: 'Synthesis and coronary vasodilating activity of 2-substituted adenosines' Chem. Pharm. Bull., vol. 23, no. 4, 1975, pages 759-774).

-

1. Document **D1** (the references in parentheses applying to this document) discloses the vasodilatating (page 759, note 7, and 768, Table V, last column) 2-Substituted adenosine compounds **29j** and **29k** (page 768, Table V), which are pyrazole substituted derivatives of adenosine of the formula as disclosed in claim 1 of the application, wherein R^2 and R^4 are either both CH_3 (compound **29j**) or CH_3 and Benzyl (compound **29k**).

2. The subject-matter of claim 1 therefore **differs** from these known compounds in that either R^2 or R^4 is hydrogen (see the proviso of claim 1).

3. The subject-matter of **claim 1** is therefore **novel** (Article 33(2) PCT).

4. The **problem** to be solved by the present invention may therefore be regarded as to find alternative vasodilatating compounds.

5. The **solution** to this problem proposed in **claim 1** of the present application is considered as involving an **inventive** step (Article 33(3) PCT), because the compounds **29j** and **29k** are either not (**29j**) or very poor (**29k**) vasodilatating compounds (see Table V, page 768: the Coronary dilator potency of these compounds is nil or very low (0.13)). Therefore, the application overcomes a technical prejudice by using pyrazole substituted adenosines as vasodilatating agents, and the subject-matter of claim 1 is considered inventive (Article 33(3) PCT).

6. **Claims 2 to 17 and 19** are dependent on claim 1 and as such also meet the requirements of the PCT with respect to **novelty** and **inventive** step.

7. A method using these new and inventive compounds, or a pharmaceutical composition comprising them is considered new and inventive.

Therefore, the subject-matter of **claims 20 to 25** is considered **new** (Article 33(2) PCT) and **inventive** (Article 33(3) PCT).

8. The compounds disclosed in claims 1-17 and 19 have an application as being comprised in a pharmaceutical composition (claims 23-25).

Therefore, the subject-matter of **claims 1-17, 19 and 23-25** complies with the requirements of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document **D1** is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

1. **Claims 3 to 17** are not supported by the description as required by Article 6 PCT, for the following reasons:

1.1 The features of claims 3 to 6, 8, 12 to 14, 16 and 17, that R^3 is selected from

said particular groups disclosed in said claims, is not referred to in the description.

1.2 The features of claims 3 to 5 that R^5 and R^6 are selected from said particular groups disclosed in said claims, is not referred to in the description.

1.3 The features of claims 3 to 11 and 13 to 16, that R^7 is selected from said particular groups disclosed in said claims, is not referred to in the description.

1.4 The features of claims 8, 13 and 14, that R^8 is selected from said particular groups disclosed in said claims, is not referred to in the description.

2. **Claim 1** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined:

the substituent R^{23} is not defined in said claim (see claim 1, page 1 of the claim, lines 7, 14 and 25, and page 2 of the claim, lines 11 and 23).

3. The description does not meet the requirements of **Article 5 PCT** in that the invention is not clearly defined: the substituent R^{23} is not defined (see page 4, lines 9 and 16, and see page 5, lines 1, 13 and 25) in the description. This cannot be considered as an obvious spelling mistake (the substituents R^{20} and R^{22} for instance have different meanings (see from page 5, line 31 to page 6, line 7), the description gives therefore obviously the impression that R^{23} would have yet another meaning).

4. The expression "**and C_{1-6}**" used in **claim 5** is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers; thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). (It is obvious that "**C_{1-6} alkyl**" is meant here, according to the definition of R^5 and R^6 in claim 1).

5. The expression "alkyl or aryl or heteroaryl amide" used in **claim 1** (see the definitions of R^3, R^5, R^6, R^7, R^8, R^{20} and R^{22}) is unclear (the description on page 5, line 5 suggests that "alkylamide, arylamide and heteroarylamide" are meant here) and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

6. **Claim 18** is vague and unclear (according to claim 10, R^1 is CH_2OH, it cannot be at the same time CONHEt) and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

7. **Claim 20** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved ("a therapeutically effective amount ... sufficient to ...") which merely amounts to a statement of the underlying problem.

8. The expressions "for stimulating coronary vasodilatation in a mammal" and "for the purpose of imaging the heart" used in **claim 20** are vague and unclear (Is the method claimed a method of imaging the heart?, or a method for stimulating coronary vasodilatation in a mammal?) and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

9. The use of the expression "*incorporated by reference*" (page 34, line 11 and page 37, line 12) is not allowed in some designated Contracting States.

10. The embodiments of the invention described on page 18, lines 3-14 ("This invention also includes pro-drugs...") do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

11. Attention is drawn to the following spelling mistakes:

Claim 12: "R_3 is",
Claim 13: the ";" between "and aryl" and "that is",
page 4, line 18, page 5, lines 3, 15 and 27: "**substituted**",
page 6, line 3: "$_{C2-15}$",
page 6, line 20: "substituent **that** is",
page 7, line 6: "from **of**",
page 7, line 10: "aryl **in** that **aryl** is",
page 7, line 17: "C_{1-3} and",
page 20, line 7: "heated **heated**",
page 22, line 15: "The mixture heated" and "at 65°C **in** for 24 h.",
page 26: There is no **Example 12** disclosed,
page 23, line 5: "dissolved one equivalent of",
page 31, line 4: "potency Compound 16" and "and compared".

TITLE: N-Pyrazole A_{2A} Receptor Agonists

Background Of The Invention

Field of Invention

This invention includes N-pyrazole substituted 2-adenosine compounds that are useful as A_{2A} receptor agonists. The compounds of this invention are vasodilating agents that are useful as heart imaging aids that aid in the identification of mammals, and especially humans who are suffering from coronary disorders such poor coronary perfusion which is indicative of coronary artery disease (CAD). The compounds of this invention can also be used as therapeutics for coronary artery disease as well as any other disorders mediated by the A_{2A} receptor.

Description of the Art

Pharmacological stress is frequently induced with adenosine or dipyridamole in patients with suspected CAD before imaging with T1 scintigraphy or echocardiography. Both drugs effect dilation of the coronary resistance vessels by activation of cell surface A_2 receptors. Although pharmacological stress was originally introduced as a mean of provoking coronary dilation in patients unable to exercise, several studies have shown that the prognostic value of ^{201}T1 or echocardiographic imaging in patients subjected to pharmacological stress with adenosine or dipyridamole was equivalent to patients subjected to traditional exercise stress tests. However, there is a high incidence of drug-related adverse side effects during pharmacological stress imaging with these drugs such as headache and nausea, that could be improved with new therapeutic agents.

Adenosine A_{2B} and A3 receptors are involved in a mast cell degranulation and, therefore, asthmatics are not give the non-specific adenosine agonists to induce a pharmacological stress test. Additionally, adenosine stimulation of the A_1 receptor in the atrium and A-V node will diminish the S-H interval which can induce AV block (N.C. Gupto et al.; *J. Am Coll. Cardiol;* (1992) 19: 248-257). Also, stimulation of the adenosine A_1 receptor by adenosine may be responsible for the nausea since the A_1 receptor is found in the intestinal tract (J. Nicholls et al.; *Eur. J. Pharm.*(1997) 338(2) 143-150).

Animal data suggests that specific adenosine A_{2A} subtype receptors on coronary resistance vessels mediate the coronary dilatory responses to adenosine, whereas subtype A_{2B} receptor stimulation relaxes peripheral vessels (note: the latter lowers systemic blood

pressure). As a result there is a need for pharmaceutical compositions that are A_{2A} receptor agonists that have no pharmacological effect as a result of stimulating the A_1 receptor *in vivo*. Furthermore, there is a need for A_{2A} receptor agonists that have a short half-life, and that are well tolerated by patients undergoing pharmacological coronary stress evaluations.

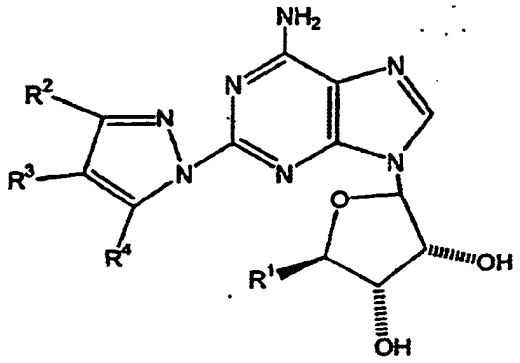
SUMMARY OF THE INVENTION

In one aspect, this invention includes 2-adenosine N-pyrazole compounds that are useful A_{2A} receptor agonists.

In another aspect, this invention includes pharmaceutical compounds including 2-adenosine N-pyrazole that are well tolerated with few side effects.

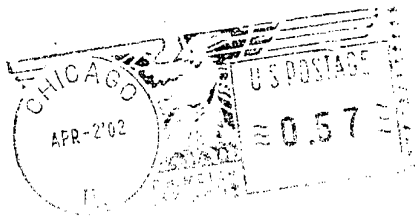
Still another aspect of this invention are N-pyrazole compounds that can be easily used in conjunction with radioactive imaging agents to facilitate coronary imaging.

In one embodiment, this invention includes 2- adenosine N-pyrazole compounds having the following formula:



In another embodiment, this invention includes methods for using compounds of this invention to stimulate coronary vasodilatation in mammals, and especially in humans, for stressing the heart induced steal situation for purposes of imaging the heart.

In still another embodiment, this invention is a pharmaceutical composition comprising one or more compounds of this invention and one or more pharmaceutical excipients.



PCT/US00/40281

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300 South Wacker Drive
Chicago, Illinois 60606-6709

Commissioner for Patents
Box PCT
Washington, D.C. 20231

PATENT COOPERATION TREATY

DOCKETED

OCT 23 2001

PCT DUE DATE: BY:

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HUGHES, A. Blair
McDONNELL BOEHNEN HULBERT
& BERGHOFF
300 South Wacker Drive
Chicago, IL 60606
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.10.2001
Applicant's or agent's file reference: 99,423-A	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/40281	21/06/2000	22/06/1999

Applicant
CV THERAPEUTICS, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ferro Vasconcelos, M Tel.+49 89 2399-7[illegible] 8101

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
99,423-A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/40281	21/06/2000	22/06/1999
International Patent Classification (IPC) or national classification and IPC C07H19/16		
Applicant CV THERAPEUTICS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/01/2001	12.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Jenn, T Telephone No. +49 89 2399 7348

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/40281

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

3-43	as originally filed			
1,2	as received on	28/06/2001	with letter of	26/06/2001

Claims, No.:

1-25	as originally filed

Drawings, sheets:

1/4-4/4	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 18,20-22.

because:

   ☒ the said international application, or the said claims Nos. 20-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 18 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17,19-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17,19-25
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17,19,23-25
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

1. The amendments filed with the letter dated June 26, 2001, received on June 28, 2001, introduce subject-matter which extend beyond the content of the application as filed, contrary to Article 34(2) PCT. The amendments concerned are the following:

1.1 Amended claim 1 (**see particularly Item VIII § 3 of this opinion**):

A compound having the formula as claimed in claim 1, wherein R^3 is selected from "$NR^{20}C(NR^{20})NH\mathbf{R^{22}}$" (line 7, new page 47), or wherein substituents are optionally substituted with "$NR^{20}C(NR^{20})NH\mathbf{R^{22}}$" (line 14, new page 47) is not disclosed in the application as originally filed which discloses such a compound wherein R^3 is "$NR^{20}C(NR^{20})NH\mathbf{R^{23}}$" (line 7, page 44), or wherein substituents are optionally substituted by "$NR^{20}C(NR^{20})NH\mathbf{R^{23}}$" (line 14, page 44).

A compound having the formula as claimed in claim 1, wherein the substituents of R^7 are optionally substituted with "$NR^{20}C(NR^{20})NH\mathbf{R^{22}}$" (line 13, new page 48) is not disclosed in the application as originally filed which discloses such a compound wherein substituents are optionally substituted by "$NR^{20}C(NR^{20})NH\mathbf{R^{23}}$" (l. 11, p. 45).

1.2 Amended claim 8:

A compound according to claim 8 wherein R^7 is selected from "**C_{1-8} alkyl that is optionally substituted with one substituent selected from halo, CF_3, CN and OR^{20}**" (lines 27-28, new page 51) is not disclosed in the application as originally filed which discloses such a compound wherein R^7 is selected from "**C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with aryl, and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3**" (page 48, lines 22-24).

1.3 Amended claim 9:

A compound according to claim 9 wherein R^7 is selected from "**C_{1-3} alkyl that is optionally substituted with one substituent selected from halo, CF_3, CN and OR^{20}**" (lines 1-2, new page 52) is not disclosed in the application as originally filed which discloses such a compound wherein R^7 is selected from "**C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with aryl, and wherein each optional aryl substituent is optionally substituted with halo**" (page 48, lines 31-33).

1.4 Amended claim 16:

A compound according to claim 16 wherein R^7 is selected from "**C_{1-3} alkyl that is optionally substituted with one substituent selected from halo, CF_3, CN and OR^{20}**" (lines 11-12, new page 53) is not disclosed in the application as originally filed

which discloses such a compound wherein R^7 is selected from "**C_{1-5}** alkyl, wherein the alkyl substituent is optionally substituted with **aryl, and wherein each optional aryl substituent is optionally substituted with halo**" (page 50, lines 11-13).

1.5 Amended description:

The same as disclosed in § 1.1 above applies to the corresponding amendments in the description (new page 4, line 16; new page 5, lines 1, 13 and 25).

A compound wherein "when R^1=CH_2OH, then it is most preferred that R^7 is a methyl and R_3 is CO_2Et" (see new page 8, line 29) is not disclosed in the application as originally filed (see original claims 11 and 12 which depend on claim 10).

2. As some of the amendments of the description are not allowable (see above), and as said amendments were not made by the way of **replacement pages** in the manner stipulated by Rule 66.8(a) PCT (see as well the PCT Guidelines Chap. VI-7.2 and 7.3), certain of the allowable amendments of the description cannot be taken into consideration in this report (the numbering of the pages would become confusing).

Therefore, although the amendments of the description from new page 5 (line 27) to new page 8 (line 28), and from new page 8 (line 31) to new page 9 (line 28) do not introduce subject-matter which was not disclosed in the application as originally filed, these amendments are not taken in consideration in this report, nor are taken the allowable amendments of the description on new page 10 (lines 5 and 9), on new page 23 (line 7), on new page 25 (line 15), on new page 26 (line 5 [Obs: "is" should be replaced by "in"]), on new page 29 (line 10), on new page 30 (line 1), on new page 31 (line 1), on new page 34 (line 1), on new page 37 (line 1), and on new page 40 (line 1).

3. Therefore, the present opinion will be given on the subject-matter of claims 1-25 as originally filed, on the subject-matter of amended pages 1-2 of the description as filed with the letter dated June 26, 2001, received on June 28, 2001, which replace the original pages 1-2, and on original pages 3 to 43 of the description.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject-matter of **claim 18** is so unclear (see the grounds for this objection in

Item VIII of this opinion), that no meaningful opinion can be formed on the novelty, inventive step and industrial applicability of said claim.

2. The method as claimed in **claims 20 to 22** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (diagnostic method carried out on the living human or animal body). Consequently, **no opinion** will be formulated **on** the **industrial applicability** of the subject-matter of these claims (Article 34(4)(a)(i) PCT, see also the PCT-guidelines IV-2.4.(d) and IV-2.5); an opinion on novelty and inventive step will be given for the alleged effects of a compound of claim 1 in the method of claims 20 to 22.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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Reference is made to the following document:

D1 (R. MARUMOTO et al.: 'Synthesis and coronary vasodilating activity of 2-substituted adenosines' Chem. Pharm. Bull., vol. 23, no. 4, 1975, pages 759-774).

-

1. Document **D1** (the references in parentheses applying to this document) discloses the vasodilatating (page 759, note 7, and 768, Table V, last column) 2-Substituted adenosine compounds **29j** and **29k** (page 768, Table V), which are pyrazole substituted derivatives of adenosine of the formula as disclosed in claim 1 of the application, wherein R^2 and R^4 are either both CH_3 (compound **29j**) or CH_3 and Benzyl (compound **29k**).

2. The subject-matter of claim 1 therefore **differs** from these known compounds in that either R^2 or R^4 is hydrogen (see the proviso of claim 1).

3. The subject-matter of **claim 1** is therefore **novel** (Article 33(2) PCT).

4. The **problem** to be solved by the present invention may therefore be regarded as to find alternative vasodilatating compounds.

5. The **solution** to this problem proposed in **claim 1** of the present application is considered as involving an **inventive** step (Article 33(3) PCT), because the compounds **29j** and **29k** are either not (**29j**) or very poor (**29k**) vasodilatating compounds (see Table V, page 768: the Coronary dilator potency of these compounds is nil or very low (0.13)). Therefore, the application overcomes a technical prejudice by using pyrazole substituted adenosines as vasodilatating agents, and the subject-matter of claim 1 is considered inventive (Article 33(3) PCT).

6. **Claims 2 to 17 and 19** are dependent on claim 1 and as such also meet the requirements of the PCT with respect to **novelty** and **inventive** step.

7. A method using these new and inventive compounds, or a pharmaceutical composition comprising them is considered new and inventive.

Therefore, the subject-matter of **claims 20 to 25** is considered **new** (Article 33(2) PCT) and **inventive** (Article 33(3) PCT).

8. The compounds disclosed in claims 1-17 and 19 have an application as being comprised in a pharmaceutical composition (claims 23-25).

Therefore, the subject-matter of **claims 1-17, 19 and 23-25** complies with the requirements of Article 33(4) PCT.

Re Item VII
Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document **D1** is not mentioned in the description, nor is this document identified therein.

Re Item VIII
Certain observations on the international application

1. **Claims 3 to 17** are not supported by the description as required by Article 6 PCT, for the following reasons:

1.1 The features of claims 3 to 6, 8, 12 to 14, 16 and 17, that R^3 is selected from

said particular groups disclosed in said claims, is not referred to in the description.

1.2 The features of claims 3 to 5 that R^5 and R^6 are selected from said particular groups disclosed in said claims, is not referred to in the description.

1.3 The features of claims 3 to 11 and 13 to 16, that R^7 is selected from said particular groups disclosed in said claims, is not referred to in the description.

1.4 The features of claims 8, 13 and 14, that R^8 is selected from said particular groups disclosed in said claims, is not referred to in the description.

2. **Claim 1** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined:

the substituent **R^{23}** is not defined in said claim (see claim 1, page 1 of the claim, lines 7, 14 and 25, and page 2 of the claim, lines 11 and 23).

3. The description does not meet the requirements of **Article 5 PCT** in that the invention is not clearly defined: the substituent **R^{23}** is not defined (see page 4, lines 9 and 16, and see page 5, lines 1, 13 and 25) in the description. This cannot be considered as an obvious spelling mistake (the substituents R^{20} and R^{22} for instance have different meanings (see from page 5, line 31 to page 6, line 7), the description gives therefore obviously the impression that R^{23} would have yet another meaning).

4. The expression "**and C_{1-6}**" used in **claim 5** is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). (It is obvious that "**C_{1-6} alkyl**" is meant here, according to the definition of R^5 and R^6 in claim 1).

5. The expression "alkyl or aryl or heteroaryl amide" used in **claim 1** (see the definitions of R^3, R^5, R^6, R^7, R^8, R^{20} and R^{22}) is unclear (the description on page 5, line 5 suggests that "alkylamide, arylamide and heteroarylamide" are meant here) and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

6. **Claim 18** is vague and unclear (according to claim 10, R^1 is CH_2OH, it cannot be at the same time CONHEt) and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

7. **Claim 20** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved ("a therapeutically effective amount ... sufficient to ...") which merely amounts to a statement of the underlying problem.

8. The expressions "for stimulating coronary vasodilatation in a mammal" and "for the purpose of imaging the heart" used in **claim 20** are vague and unclear (Is the method claimed a method of imaging the heart?, or a method for stimulating coronary vasodilatation in a mammal?) and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

9. The use of the expression "*incorporated by reference*" (page 34, line 11 and page 37, line 12) is not allowed in some designated Contracting States.

10. The embodiments of the invention described on page 18, lines 3-14 ("This invention also includes pro-drugs...") do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

11. Attention is drawn to the following spelling mistakes:

Claim 12: "$\mathbf{R_3}$ is",
Claim 13: the "**;**" between "and aryl" and "that is",
page 4, line 18, page 5, lines 3, 15 and 27: "**substituted**",
page 6, line 3: "$_{C2\text{-}15}$",
page 6, line 20: "substituent **that** is",
page 7, line 6: "from **of**",
page 7, line 10: "aryl **in** that **aryl** is",
page 7, line 17: "$C_{1\text{-}3}$ and",
page 20, line 7: "heated **heated**",
page 22, line 15: "The mixture heated" and "at 65°C **in** for 24 h.",
page 26: There is no **Example 12** disclosed,
page 23, line 5: "dissolved one equivalent of",
page 31, line 4: "potency Compound 16" and "and compared".

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78779 A2

(51) International Patent Classification[7]: C07H 19/16, A61K 31/7076, 49/00, A61P 9/00

(21) International Application Number: PCT/US00/40281

(22) International Filing Date: 21 June 2000 (21.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/338,185 22 June 1999 (22.06.1999) US

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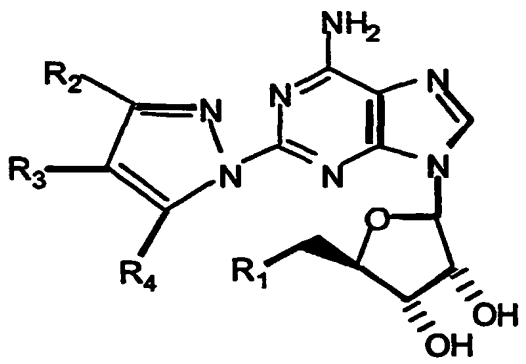
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: N-PYRAZOLE A_2A RECEPTOR AGONISTS



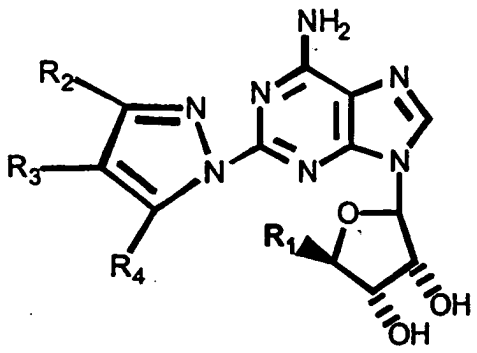
(1)

(57) Abstract: 2-Adenosine N-pyrazole compounds having formula (1) and methods for using compounds as A2A receptor agonists to stimulate mammalian coronary vasodilatation for therapeutic purposes and for purposes of imaging the heart.

WO 00/78779 A2

What we claim is:

1. A compound having the formula:



wherein $R^1 = CH_2OH$, $-CONR_5R_6$;

R^3 is selected from the group consisting of C_{1-15} alkyl, halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$,-$CONR^7R^8$, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^5 and R^6 are each individually selected from H, C_1-C_{15} alkyl optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and

$OCON(R^{20})_2$ and wherein optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^7 is selected from the group consisting of hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$ and $OCON(R^{20})_2$ and wherein optional heteroaryl, aryl and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^{20} is selected from the group consisting of H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl;

R^{22} is selected from the group consisting of C_{1-15} alkyl, $_{C2-15}$ alkenyl, C_{2-15} alkynyl,

heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl; and

wherein R^2 and R^4 are selected from the group consisting of H, C_{1-6} alkyl and aryl optionally substituted with halo, CN, CF_3, OR^{20} and $N(R^{20})_2$, with the proviso that when R^2 is not hydrogen then R^4 is hydrogen, and when R^4 is not hydrogen then R^2 is hydrogen.

2. The compound of claim 1 wherein R^3 is selected from the group consisting of C_{1-15} alkyl, halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, COR^{20}, CO_2R^{20}, -$CONR^7R^8$, aryl and heteroaryl wherein the alkyl, aryl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, COR^{20}, CO_2R^{20} and $CON(R^{20})_2$, and wherein each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^5 and R^6 are each individually selected from the group consisting of H, and C_1-C_{15} alkyl optionally substituted with one aryl substituent that is optionally substituted with halo or CF_3;

R^7 is selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkynyl, aryl, and heteroaryl, wherein the alkyl, alkynyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, CF_3, CN, and OR^{20}, and wherein each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen and C_{1-15} alkyl;

R^{20} is selected from the group consisting of H, C_{1-4} alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with one alkyl substituent; and

R^{22} is selected from the group consisting of C_{1-4} alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with from 1 to 3 alkyl groups.

3. The compound of claim 1 wherein R^3 is selected from the group consisting of C_{1-15} alkyl, halo, CF_3, CN, OR^{20}, CO_2R^{20} , -$CONR^7R^8$, aryl and heteroaryl, wherein the alkyl, aryl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, aryl, CF_3, CN, OR^{20}, CO_2R^{20} or $CON(R^{20})_2$, and wherein each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^5 and R^6 are each individually selected from hydrogen and C_{1-6} alkyl;

R^7 is selected from the group consisting of C_{1-10} alkyl, aryl, and heteroaryl, wherein the alkyl, aryl and heteroaryl substituents are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, heteroaryl, CF_3, CN, and OR^{20}, and wherein each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen and C_{1-15} alkyl; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

4. The compound of claim 1 wherein R^3 is selected from the group consisting of C_{1-10}, alkyl, halo, CF_3, CN, CO_2R^{20}, -$CONR^7R^8$, aryl and heteroaryl wherein the alkyl, aryl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, CF_3, CN, OR^{20} and $CON(R^{20})_2$;

R^5 and R^6 are each individually selected from hydrogen and C_{1-6} alkyl;

R^7 is selected from the group consisting of C_{1-10} alkyl, aryl, and heteroaryl, wherein the alkyl, aryl and heteroaryl substituents are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, heteroaryl, CF_3, CN, OR^{20} and wherein each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from hydrogen and C_{1-15} alkyl; and

R^{20} is selected from hydrogen and C_{1-4} alkyl.

5. The compound of claim 1 wherein R^3 is selected from the group consisting of C_{1-10} alkyl, halo, CF_3, CN, OR^{20}, CO_2R^{20}, -$CONR^7R^8$ and aryl; wherein the alkyl and aryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, CF_3, CN, OR^{20} and $CON(R^{20})_2$;

R^5 and R^6 are each individually selected from hydrogen and C_{1-6};

R^7 is selected from the group consisting of C_{1-10} alkyl, aryl, and heteroaryl, where the alkyl, aryl and heteroaryl substituents are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, heteroaryl, CF_3, CN, OR^{20} and wherein each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from hydrogen and C_{1-15} alkyl; and

R^{20} is selected from hydrogen and C_{1-4} alkyl.

6. The compound of claim 1 wherein $R^1 = CH_2OH$;

R^3 is selected from the group consisting of CO_2R^{20}, -$CONR^7R^8$ and aryl; wherein the aryl substituent is optionally substituted with from 1 to 3 substituents independently selected

from the group consisting of halo, C_{1-6} alkyl, CF_3, CN, OR^{20}, and $CON(R^{20})_2$;

R^7 is selected from the group consisting of hydrogen, C_{1-10} alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, CF_3, CN, OR^{20} and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from hydrogen and C_{1-15} alkyl; and

R^{20} is selected from hydrogen and C_{1-4} alkyl.

7. The compound of claim 1 wherein $R^1 = CH_2OH$;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$ and aryl wherein the aryl substituent is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-8} alkyl, wherein the alkyl substituent is optionally substituted with one substituent selected from aryl, CF_3, CN, and OR^{20} and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, or OR^{20};

R^8 is selected from hydrogen and C_{1-8} alkyl; and

R^{20} is selected from hydrogen and C_{1-4} alkyl.

8. The compound of claim 1 wherein $R^1 = CH_2OH$;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group of halo, C_{1-3} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with aryl, and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3;

R^8 is selected from hydrogen and C_{1-3} alkyl; and

R^{20} is selected from hydrogen and C_{1-4} alkyl.

9. The compound of claim 1 wherein $R^1 = CH_2OH$;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group of halo, C_{1-3} alkyl, and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with aryl, and wherein each optional aryl substituent is optionally substituted with halo;

R^8 is hydrogen; and

R^{20} is selected from hydrogen and C_{1-4} alkyl.

10. The compound of claim 1 wherein $R^1 = CH_2OH$;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from halo, C_{1-3} alkyl and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with aryl, and wherein each optional aryl substituent is optionally substituted with halo;

R^8 is hydrogen; and

R^{20} is selected from hydrogen and C_{1-4} alkyl.

11. The compound of claim 10 wherein R^7 is a methyl.

12. The compound of claim 10 wherein R_3 is $-CO_2Et$.

13. The compound of claim 1 wherein $R^1 = -CONHEt$;

R^3 is seleeted from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl; that is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3, CN, OR^{20}, and $CON(R^{20})_2$;

R^7 is selected from the group consisting of hydrogen, C_{1-10} alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, CF_3, CN, and OR^{20} and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from hydrogen, and C_{1-15} alkyl; and

R^{20} is selected from hydrogen, and C_{1-4} alkyl.

14. The compound of claim 1 wherein $R^1 = -CONHEt$;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl, and aryl, wherein the alkyl and aryl substituents are optionally substituted with one substituent selected from the group consisting of halo, aryl, CF_3, CN, OR^{20} and each optional aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from hydrogen, and C_{1-8} alkyl; and

R^{20} is selected from hydrogen, and C_{1-4} alkyl.

15. The compound of claim 1 wherein $R^1 = -CONHEt$;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is

optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-3} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with aryl, and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3;

R^8 is selected from hydrogen, and C_{1-3} alkyl; and

R^{20} is selected from hydrogen, and C_{1-4} alkyl.

16. The compound of claim 1 wherein R^1 = -CONHEt;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from halo, C_{1-3} alkyl and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-5} alkyl, wherein the alkyl substituent is optionally substituted with aryl, and wherein each optional aryl substituent is optionally substituted with halo;

R^8 is hydrogen; and

R^{20} is selected from hydrogen, and C_{1-4} alkyl.

17. The compound of claim 1 wherein R^1 = -CONHEt;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from halo, C_{1-3} alkyl and OR^{20};

R^7 is selected from hydrogen, and C_{1-3} alkyl;

R^8 is hydrogen; and

R^{20} is selected from hydrogen, and C_{1-4} alkyl.

18. The compound of claim 10 where R^1 is –CONHEt.

19. A compound matter of claim 1 wherein the compound is selected from ethyl1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl)-pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)-oxolane-3,4-diol, (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide, 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid, (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N,N-dimethylcarboxamide, (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide, 1-{9-

[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxamide, 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-(cyclopentylmethyl)carboxamide, (1-{9-[(4S,2R, 3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-[(4-chlorophenyl)methyl]carboxamide, Ethyl 2-[(1-{9-[(4S,2R, 3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)carbonylamino]acetate, and mixtures thereof.

20. A method for stimulating coronary vasodilatation in a mammal by administering to the mammal a therapeutically effective amount of a compound of claim 1 that is sufficient to stress the heart and induce a coronary steal situation for the purposes of imaging the heart.

21. The method of claim 20 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.

22. The method of claim 20 wherein the mammal is a human.

23. A pharmaceutical composition comprising the compound of claim 1 and one or more pharmaceutical excipients;

24. The pharmaceutical composition of claim 23 wherein the pharmaceutical composition is in the form of a solution.

25. The pharmaceutical composition of claim 23 wherein the composition is useful as an anti-inflammatory, in adjunctive therapy with angioplasty, as a platelet aggregation inhibitor, and as an inhibitor of platelet and neutrophil activation.